IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

ERIC A. FORSSEN v. ROLF J. MEHLHORN	Interference No. 103,469 Administrative Patent Judge: Ronald H. Smith

BOX INTERFERENCE
Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

JUNIOR PARTY FORSSEN'S OPENING BRIEF FOR FINAL HEARING UNDER 37 C.F.R. § 1.656

STATEMENT OF INTEREST

The full name of the party represented by the undersigned attorney is Eric A. Forssen, and the real party in interest is NeXstar Pharmaceuticals, Inc. At the time this interference was declared, the involved Forssen application was assigned to Vestar, Inc. During the course of the interference, as noted in a paper filed February 6, 1995, Vestar, Inc. merged with Nexagen, Inc. The merged companies became NeXstar Pharmaceuticals, Inc., the current assignee of the Forssen application.

STATEMENT OF RELATED CASES

The present interference has not been previously before the Board of Patent Appeals and Interferences, and there are no related appeals or interferences or actions pending before or previously decided by the Board of Patent Appeals and Interferences, the U.S. Court of Appeals for the Federal Circuit, or a district court.

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STATEMENT OF THE ISSUES PRESENTED FOR DECISION

Whether Mehlhorn can demonstrate that Administrative Patent Judge Ronald H. Smith exhibited an abuse of discretion in the Decision on Motions and Order to Show Cause of October 4, 1996 (Paper No. 58) in which he found that:

- Mehlhorn's claims 27-50, corresponding to the count, are unpatentable to Mehlhorn under 35 U.S.C. §§ 102 and 103 and, accordingly,
    - granted Forssen's motion for judgment under 37 C.F.R. § 1.633(a) (Motion 3);
- Mehlhorn's proposed claims 51-55 are not patentable to Mehlhorn in view of the decision that claims 27-50, on which the proposed claims depend, are not patentable to Mehlhorn, because no separate basis for patentability is asserted, and accordingly,
    - denied Mehlhorn's contingent motion to redefine the interfering subject matter under 37 C.F.R. § 1.633(c)(2) and 1.633(i) (Motion 5) and
    - deferred (although agreeing with) Forssen's contingent motion for judgment under 37 C.F.R. § 1.633(a) (Motion 6); and
- Forssen's claims 5, 6, and 25-27 do not correspond to the count and, accordingly,
    - granted Forssen's motion to redefine the interfering subject matter under 37 C.F.R. § 1.633(c)(4) (Motion 2).

STATEMENT OF THE FACTS

The Patent and Application in Interference

1. The party Eric A. Forssen (hereinafter "Forssen") received U.S. Patent No. 4,946,683 ("the '683 patent"), on August 7, 1990. In the Notice of Interference (set forth in the Record for the Party Forssen, volume I, tab 1),[1] the '683 patent was accorded benefit of parent application, USSN 07/122,354, which was filed on November 11, 1987.

2. The party Rolf J. Mehlhorn ("Mehlhorn") is in the Interference with a pending application, USSN 07/741,305, that was filed August 7, 1991. In the Notice of Interference (FR vol 1, tab 1), that application was accorded benefit of its earliest parent application, USSN 06/776,826, which was filed on September 17, 1985.

History of the Interference

3. During prosecution of the Mehlhorn application, Mehlhorn sought to institute an interference with the Forssen '683 patent, beginning with a Request by Applicant for Interference Pursuant to 37 C.F.R. § 1.607 and Preliminary Amendment, filed August 7, 1991 (Paper No. 3) and ending with an Amendment and Renewed Request for Interference, filed April 22, 1994 (Paper No. 16). The Interference was declared on October 11, 1994.

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[1] The Record for Party Forssen shall be designated "FR," with the specific volume set forth as "vol _" with either the appropriate page or tab number. The Record for the Party Mehlhorn shall be set forth as "MR" with the appropriate page number.

4. In this Interference, both parties moved for judgment on the grounds of unpatentability, with each alleging that the claims of the other were unpatentable under 35 U.S.C. §§ 102 and 103.

5. Forssen asserted that Mehlhorn claims 27-50 were anticipated by and/or obvious over a 1976 publication by J.W. Nichols and D.W. Deamer[2] as well as a 1977 publication by J.A. Cramer and J.H. Prestegard[3] and, in support of the motion, submitted declarations by both Dr. Nichols and Dr. Prestegard (FR vol II). Mehlhorn asserted that Forssen claims 1-27 were anticipated by and/or obvious over either of two references by Mayer et al.[4] as well as the Hope patent[5] and, in support of the motion, submitted declarations by Dr. David S. Cafiso (MR 1-64).

6. In the Decision on Motions of October 4, 1996, the Administrative Patent Judge granted Forssen's motion and found that Mehlhorn claims 27-50 were unpatentable to Mehlhorn. The Administrative Patent Judge also granted Mehlhorn's motion as it applied to Forssen

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[2] Nichols, J.W. and Deamer, D.W., "Catecholamine Uptake and Concentration by Liposomes Maintaining pH Gradients," Biochimica et Biophysica Acta, 455:269-271 (1976) ("Nichols") (FR Exh 3).

[3] Cramer, J.A. and Prestegard, J.H., "NMR Studies of pH-Induced Transport of Carboxylic Acids Across Phospholipid Vesicle Membranes," Biochemical and Biophysical Research Communications, 75(2):295-301 (1977) ("Cramer") (FR Exh 5).

[4] Mayer et al., "Techniques for Encapsulating Bioactive Agents into Liposomes," Chemistry and Physics of Lipids 40:333-345 (1986) (MR Exh 6) and Mayer et al., "Uptake of Adriamycin into Large Unilamellar Vesicles in Response to a pH Gradient," Biochimica et Biophysica Acta, 857:123-126 (1986). (Although cited in Mehlhorn's papers as Exh 7, this exhibit does not correspond to MR Exh 7)

[5] Hope et al., U.S. Patent No. 5,204,112, issued April 20, 1993 and filed on June 12, 1987. (MR Exh 8).

claims 1-4 and 7-24, noting that Forssen had conceded that its claims 1-4 and 7-24 were not patentable in light of the Nichols and Cramer references and having also found, in response to a motion by Forssen, that claims 5, 6, and 25-27 were separately patentable to Forssen.

7. Mehlhorn also moved to redefine the interfering subject matter by adding claims 51-55 to be designated as corresponding to the count. In the Decision on Motions, the Administrative Patent Judge denied that motion, noting that Mehlhorn merely contended that these claims recited the "same patentable features as Mehlhorn claim 27." Because claim 27 was unpatentable, the Administrative Patent Judge found that Mehlhorn had not shown that proposed claims 51-55 were patentable to Mehlhorn. The Administrative Patent Judge also noted his agreement with Forssen that the claims were not patentable for the reasons set forth in Forssen's contingent motion for judgment.

8. Forssen moved to redefine the interfering subject matter by designating Forssen's claims 5, 6 and 25-27 as not corresponding to the count. The Administrative Patent Judge granted that motion and redeclared the interference on that basis.

9. The Decision on Motions also set forth an Order to Show Cause, directed to both parties. In response, Mehlhorn requested a final hearing to address the issues decided adversely to it and favorably to Forssen. Forssen did not file a response to that Order.

The Technology

10. The Forssen patent and Mehlhorn application relate to a method of loading liposomes with charged chemical species, such as drugs, by creating a pH gradient to drive the chemical species into the liposomes.

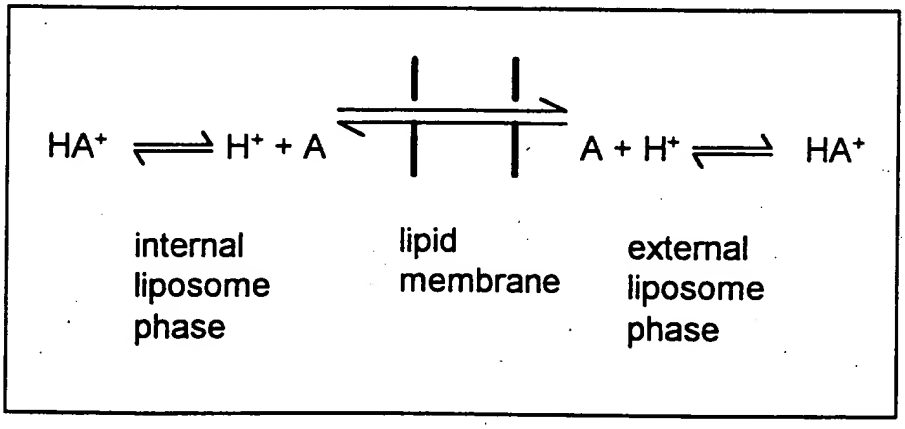
11. Liposomes are tiny, fluid-filled spherical particles or vesicles formed by one or more lipid membranes. The lipid membranes are typically made of phospholipid molecules which have hydrophilic polar head groups that seek water and hydrophobic lipid tails that repel water. Upon exposure to water, the phospholipid molecules spontaneously arrange into spherical particles in which the shell is, typically, a bilayer membrane with the lipid tails of the molecules directed toward the center of the membrane and the opposing polar heads forming the inner and outer surfaces of the bilayer membrane, as set forth in the illustration attached at Tab 1. The liposomes entrap in their interior the aqueous medium in which they are formed. (See Nichols Declaration at ¶ 7, FR vol II, tab 6 at 4-5; Prestegard Declaration at ¶ 9, FR vol II, tab 8, at 15-16.)

12. Chemical species that are uncharged, i.e., neutral, can cross through the bilayer liposome membrane, while charged chemical species cannot penetrate the bilayer membrane due to the polar inner and outer surfaces. (See Nichols Declaration at ¶ 7, FR vol II, tab 6 at 4-5; Prestegard Declaration at ¶ 9, FR vol II, tab 8 at 15-16.) In addition, the chemical species can either be positively charged, i.e., cationic, or can be negatively charged, i.e., anionic. (Mehlhorn specification, pp. 9-10).

13. When the chemical species to be loaded is a cationic chemical species, liposomes are formed in an acidic aqueous medium (which may already contain the cationic charged chemical species or to which the cationic charged chemical is added after formation of the liposomes) and a base is added to the external aqueous medium to induce the cationic chemical species to move into the liposome. (See Nichols Declaration at ¶ 7, FR vol II, tab 6 at 4; Prestegard Declaration at ¶ 10, FR vol II, tab 8 at 16-17.)

14. The force which drives the cationic chemical species into the liposome results from a change in the concentration of H^- (hydrogen ions) in the acidic external medium relative to the concentration of H^+ in the internal medium, i.e., a pH gradient. (See Nichols Declaration at ¶ 7, FR vol II, tab 6 at 4-5; Prestegard Declaration at ¶ 10, FR vol II, tab 8 at 16-17.)

15. More specifically, prior to addition of the base to the external medium, the cationic chemical species exists in two states, both outside and inside the liposome. In one state, the chemical species is in its cationic charged form (HA^+) and, in the other, it is in its uncharged form (A). These two forms exist in equilibrium in the external phase outside the liposome and also in the internal phase within the liposome. Because the uncharged form of the chemical species is freely permeable through the liposome membrane, it exists in equal concentrations on both sides of the lipid membrane. These conditions may be represented graphically as follows:



wherein A is the uncharged form of the chemical species,

HA^+ is the positively charged (cationic) form, and

H^+ represents positively charged free hydrogen ions from dissociated acid.

(See Prestegard Declaration at ¶ 10, FR vol II, tab 8 at 16-17).

16. Upon addition of the base, such as hydroxide (OH^-), to the external liposome phase, the concentration of free H^+ in that phase is lowered, i.e., free H^+ combines with the hydroxide base to form water ($H^+ + OH^- \rightarrow H_2O$). Diminishing the concentration of free H^+, i.e., raising the pH, unbalances the equilibrium in the external phase. (See Prestegard Declaration at ¶ 10, FR vol II, tab 8 at 16-17.)

17. Responding to this change in pH, the positively charged form of the chemical species (HA^+) dissociates, providing additional free H^+ (and additional uncharged material), until the equilibrium is reestablished in the external phase. The increased dissociation of the charged chemical species (HA^+) to its uncharged form (A) disrupts an equilibrium between the uncharged forms across the liposome membranes. (See Prestegard Declaration at ¶ 10, FR vol II, tab 8 at 16-17.)

18. Since dissociation creates more of the uncharged form of the chemical species in the external phase, these molecules will travel inward across the liposome membrane until equilibrium of the uncharged form of the chemical species is reestablished across the membrane. This influx results in an increase in the concentration of the uncharged chemical species inside the liposomes, which disrupts the equilibrium inside the liposome between the uncharged (A) and charged forms (HA^+) of the chemical species. To

reestablish internal equilibrium, the uncharged form of the chemical species combines with free H^+ (or H^+ from buffer) inside the liposome. This decrease in the uncharged form inside the liposomes again disrupts the equilibrium across the liposome membrane, causing even more of the uncharged form to enter the inside of the liposomes. As a result, there is an overall increase of the amount of charged form of the chemical species inside the liposome. (See Prestegard Declaration at ¶ 10, FR vol II, tab 8 at 16-17.)

19. Where the charged chemical species is anionic, i.e., negatively charged, the liposomes are formed with a basic aqueous medium (which, as above, may already contain the charged chemical species or to which the charged chemical species may be added after forming the liposomes) and an acid is added to the external aqueous medium. The added acid reduces the pH of the external medium and increases the concentration of the neutral form of the anionic chemical species, thereby inducing passage of the chemical species into the liposome. This alternative method works by an analogous mechanism to that set forth above, i.e., addition of acid to the external phase to create a pH gradient that drives the chemical species into the internal phase of the liposome. (See Nichols Declaration at ¶ 14, FR vol II, tab 6 at 7-8; Prestegard Declaration at ¶ 12, FR vol II, tab 8 at 17-18.)

The Count

20. The Count in this case (Appendix A and FR vol I, tab 3) calls for forming liposomes in an aqueous acidic medium and then driving a cationic lipophilic drug composition outside the liposome into the internal phase of the liposome by adding a base to the acidic external medium.

Mehlhorn's Claimed Invention

21. Mehlhorn's two independent claims (claims 27 and 38, set forth in Appendix B) both recite a method of preparing liposome vesicle-entrapped charged chemical species comprising three steps:

(a) forming liposomes in an aqueous medium containing either an acid or a base,

(b) adding a charged chemical species, either a cationic species or an anionic species, to the liposomes, and

(c) adding to the external liposome phase either a base or an acid to induce the chemical species to pass into the liposome's internal phase.

The claims differ only in step (c). In claim 27, step (c) speaks of inducing the chemical species to pass into the liposome's internal phase while step (c) of claim 38 adds an acid or base to create a "pH gradient between the external and internal phase" to induce the chemical species to pass into the liposome.

22. It is clear from Mehlhorn's prosecution history that both claims call for the creation of a pH gradient. For example, when faced with a rejection under 35 U.S.C. § 112, first paragraph, against claim 27 for failing to state a pH range, Mehlhorn argued:

> Initially, the Examiner is requiring recitation of pH ranges rather than merely reciting the terms "acid" and "base." Furthermore, the Examiner indicates that applicant should convey that a pH gradient is created. In response, as recognized by the Examiner, applicant notes that what is important to the present invention is not so much the absolute value of the pH of the solution used to form the vesicles or the pH of the composition added to the external

liposome phase after the vesicles are formed. **Rather, it is the creation of a pH differential which is important**.

Prosecution History of USSN 07/741,305, Paper No. 9, Amendment, March 22, 1993, at p. 6 (emphasis added).

23. Similarly in further answering the Examiner's rejection at p. 7 of that same Amendment, Mehlhorn asserted (emphasis added):

> Nonetheless, in order to expedite declaration of an interference, applicant refers the Examiner to newly added Claim 38 which recites, in step (c), "creating a pH gradient between the external liposome phase and the internal liposome phase." **Thus, what was originally implicit and inherent in Claim 27 is now set forth explicitly in newly added Claim 38**.

24. As indicated above, both independent claims 27 and 38 also expressly include both types of alternative pH gradients, depending on whether the charged chemical species is cationic or anionic. Mehlhorn has admitted that these two types of alternative pH gradients (set forth as subparts (i) and (ii) of the independent claims 27 and 38 of Mehlhorn) are patentably indistinct. For example, when the Examiner required restriction between the claims drawn to preparing liposomes by the two alternative pH gradients, Mehlhorn stated:

> The requirement for restriction is respectfully traversed in view of the fact that applicant has already, in his request for interference pursuant to 37 C.F.R. § 1.607 filed August 7, 1991, included the inventions of Group I and II in the same count. In essence, therefore, applicant has admitted on the record that the subject matter of the various claims constitutes a single patentable invention. As is set forth in MPEP § 803, restriction should not be required where an applicant acknowledges that two or more inventions are obvious over each other. *In re Lee*, 199 USPQ 108 (Comm'r Pat. 1978).

Prosecution History of USSN 07/741,305, Paper No. 13, Response to Restriction Requirement, July 23, 1993, at p. 2.

25. Moreover, in later renewing the request for interference, Mehlhorn asserted:

> In the present case, applicant has already stated on the record that the embodiment wherein a basic liposome is prepared and a pH gradient established by addition of an acid is not separately patentable from the embodiment wherein an acidic liposome is first prepared and a pH gradient established by addition of a base.

Prosecution History of USSN 07/741,305, Paper No. 16, Amendment and Renewed Request for Interference, April 22, 1994, at p. 3.

26. Significantly, Mehlhorn's independent claims 27 and 38 both recite methods of preparing a liposome vesicle-entrapped "**charged chemical species**," neither refers to a drug. Dependent claims 33-37 and 44-48, however, recite "drugs" and new proposed claims 53-55 recite specific drugs.

27. In seeking to institute the present Interference, Mehlhorn expressly admitted that there is no patentable distinction between the claims that recite a "chemical species" and those that specifically recite a "drug," stating:

> Mehlhorn does not contend that limiting the charged chemical species to a lipophilic drug constitutes a separate patentable invention. Rather, the subject claims are included to emphasize that the same patentable invention is being claimed in both the Mehlhorn application and the '683 patent.

Prosecution History of USSN 07/741,305, Paper No. 3, Request by Applicant for Interference Pursuant to 37 C.F.R. § 1.607 of August 7, 1991, at 9.

28. Finally, Mehlhorn's independent claims 27 and 38 recite the preparation of liposome "vesicle-entrapped" charged chemical species. Although the term "entrapped" is not defined, the Mehlhorn specification describes the concept in terms of "loading."

29. For example, the application is entitled:

> Improved Method for **Loading** Lipid Like Vesicles with Drugs or Other Chemicals;

the Technical Field provides that:

> The invention relates to a method for **loading** lipid-like vesicles with a drug or other chemical species by establishing a pre-imposed pH gradient. (Mehlhorn specification, p. 1);

the Disclosure of the Invention states that:

> In accordance with an embodiment of the present invention, a method is set out for **loading** lipid-like vesicles having a membrane permeable to a chemical species to be **loaded** from a **loading** solution wherein the concentration of the **loaded** chemical species within the vesicle is greater than the concentration of the chemical species in the **loading** solution and the **loaded** chemical species can be substantially maintained within the vesicle for at least one-quarter hour following **loading**. The method comprises inducing a pH gradient across the vesicle membrane while the vesicle is in the **loading** solution containing the chemical species with the pH gradient having been selected to drive the chemical species into the vesicles. (Mehlhorn specification, pp. 2-3, bridging paragraph)
>
> * * *
>
> In accordance with a second aspect of the present invention, a method is set out for **loading** lipid-like vesicles having a membrane permeable to a chemical species to be **loaded** and having the capability to maintain the **loaded** chemical species within the vesicle for at least one-quarter hour following **loading** by inducing a pH gradient across the membrane. (Mehlhorn specification, p. 3, first full paragraph)

and the Detailed Description of the Invention begins with:

> In accordance with aspects of the present invention, a method and kits are provided for quickly and efficiently l **ading** vesicles [having] a membrane permeable to a chemical species having one or more selected acid pH responsive groups or basic pH responsive groups by inducing a pH gradient across the membrane of the vesicle. (Mehlhorn specification, p. 8). (Emphasis added.)

30. There is no express definition for "loading" in the Mehlhorn specification. However, the specification suggests that "loading" is more than mere "encapsulation." Specifically, the Background discusses the many "encapsulation" techniques in the art and the many problems in the art with "encapsulating" drugs into liposomes, including, for example, low efficiency of encapsulation and the sequestration of "at best only 50%" of expensive drugs and the consequent need to recover the drugs from the drug solution. Indeed, the section concludes that "the prior art field of encapsulation methods thus has a number of very serious problems."

31. Rather than mere "encapsulation," "loading" appears to mean "accumulation," as indicated in the discussion of the invention in the Detailed Description, as follows:

> The method and the kits utilize a preimposed pH gradient between the buffer in the vesicles and the solution containing the vesicles to cause the desired chemical or drug to be **accumulated and encapsulated** by the vesicle. The general rule is that for every unit of pH difference a tenfold **accumulation** of the chemical occurs. . . .
>
> The chemicals or drugs that may be incorporated using the present method of encapsulation include those species that have acid or basic pH responsive groups, hydrophobic delocalized charged ions or that may be provided with such. The vesicle is prepared by the entrapment of a buffer which will not permeate the membrane in the preparation of the vesicle. . . .
>
> Subsequently the vesicles are treated with an alkaline or acid buffer, respectively, which will not permeate the vesicles membrane, thereby causing a pH change on the exterior but not the interior of the

vesicles. The resulting vesicles will therefore have a pH gradient between their interior and exterior. This gradient provides the driving force for **accumulating** the drug or chemical within the vesicle interior. (Mehlhorn specification, pp. 11-12). (Emphasis added.)

32. As to the extent of accumulation, the Mehlhorn specification provides that:

> The general rule is that for every unit of pH difference, a tenfold accumulation of the chemical occurs. For drugs containing several titratable groups the accumulation behavior is altered. (Mehlhorn specification at p. 11, first full paragraph).

33. As to the length of time the chemical species or drugs are to be kept within the liposome, that time period is rather modest. The Disclosure of the Invention repeatedly recites "substantially maintaining the loaded chemical species within the vesicle for at least one-quarter hour following loading." See Mehlhorn specification, pp. 2-3 and 6-7. More specifically, the Detailed Description provides that:

> After incorporation the chemical will remain in the vesicle for fifteen minutes to several hours depending on the chemicals, until the buffer leaks out of the vesicles. (Mehlhorn specification, p. 14, first full paragraph).

Indeed, the fact that the liposomes readily release the chemical species is specifically offered as an advantage of the invention, as follows:

> Also, fear of degradation of the vesicles and leakage of the chemicals prior to administration need not be a concern since the chemicals are easily encapsulated in the vesicles usually just before use, and the vesicles containing the chemicals can be immediately delivered without further purification or treatment provided the solution containing the loaded vesicles is physiologically benign. . . . Drugs encapsulated in this manner are sequestered within the vesicles (e.g., liposomes) until they reach the desired target tissue and are released when the membrane begins to break down and the drug begins to leak at the site of the desired tissue. (Mehlhorn specification, Disclosure of the Invention, pp. 7-8).

34. Each of the remaining claims depend from either claim 27 or 38. The dependent claims recite the additional elements of buffers (claims 30-32 and 41-43); loading a drug (claims 33 and 44); loading a hydrophobic drug (claims 34-37 and 45-48) and specific conditions of pH (claims 49-50).

35. In Mehlhorn's contingent motion under 37 C.F.R. §§ 1.633(c)(2) and 1.633(i) to redefine the interfering subject matter by adding claims 51-55 to be designated as corresponding to the count,[6] Mehlhorn sought to introduce claims that depended from claim 27 and recited specific acid buffers (claims 51-53) and specific cationic charged species (claims 53-55). The basis for the patentability of each of these claims is the patentability of claim 27. Specifically, Mehlhorn asserted that:

> The newly added claims all relate to species that are encompassed by Mehlhorn Claim 27. In other words, Claims 51-55 are dependent, either directly or indirectly, on Claim 27. Accordingly, Claims 51-55 all include the subject matter of Claim 27 therein. Logically, therefore, as Claim 27, corresponding to the count, has already been found by the Patent Office to be patentable over the prior art, it follows that Claims 51-55 dependent thereon are likewise patentable over the prior art.

See Mehlhorn's reply to Forssen's opposition to Mehlhorn's contingent motion to redefine the interference, at page 2. Mehlhorn also acknowledges in that same reply that it has not argued that the added claims 51-55 are separately patentable. *Id.* at 3.

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[6] Designated Motion 5 in the October 4, 1996 Decision on Motions.

The Nichols Reference

36. The reference, Nichols, J.W. and Deamer, D.W., "Catecholamine Uptake and Concentration by Liposomes Maintaining pH Gradients," Biochimica et Biophysica Acta, 455:269-271 (1976) ("Nichols") (Forssen Exh 3), is prior art to the Mehlhorn application.

37. According to Mehlhorn's declarant, Dr. David S. Cafiso, the Nichols paper is a "benchmark" that discloses the mechanism, i.e., the physical chemistry, of using a pH gradient to load catecholamines. (Third Cafiso Declaration at ¶ 3(d), MR 37). More broadly stated, Dr. Cafiso acknowledges that Nichols discloses "the physical chemistry involved in using a pH gradient to load ionizable molecules into a liposome." (Second Cafiso Declaration at ¶¶ 3(b) and 3(c), MR 18-19; Third Cafiso Declaration at ¶ 3(i), MR 43). Dr. Cafiso also recognizes that the physical chemistry disclosed by Nichols "is the physical chemistry which was then applied by Mehlhorn to produce a drug entrapped liposome composition." (Third Cafiso Declaration at ¶ 3(d), MR 37).

38. In characterizing Dr. Cafiso's third declaration, Mehlhorn recognizes that:

> Dr. Cafiso acknowledges that Nichols teaches that a drug composition can be accumulated in the liposome.

See Mehlhorn opposition to Forssen's contingent motion for judgment under 37 C.F.R § 1.633(a) that Mehlhorn claims 51-55 are unpatentable,[7] at p. 4.

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[7] Designated Motion 6 in the October 4, 1996 Decision on Motions.

39. As to the specifics of the Nichols disclosure, the paper reports the formation of liposomes in citric acid,[8] which is one of the buffers described in the Mehlhorn application (specification at p. 12) and, according to Dr. Nichols, is a buffer that is substantially impermeable through the liposomes (Nichols Declaration at ¶¶ 7-8, FR vol II, tab 6 at 4-5). Nichols then discloses the addition of the base NaOH to create a gradient of 3 pH units. Finally, three catecholamines (dopamine, epinephrine, and norepinephrine), all of which are cationic chemical species, are added to the liposomes. (Nichols Declaration at ¶¶ 7-9, FR vol II, tab 6 at 4-5).

40. The order of the last two steps, the addition of the catecholamines and the addition of the base to create the pH gradient, is not significant. Indeed, Mehlhorn has not contended otherwise. From a scientific viewpoint, the important point is that a pH gradient is established to induce the chemical species to pass from the external medium through the lipid bilayer and into the internal compartment of the liposome. The uptake or accumulation of the catecholamines through the lipid bilayer would have been expected, regardless of whether the catecholamines were added to the external medium before adding the base or the base was added to create the pH gradient before addition of the

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[8] The concentrations of the citrate and phosphate in the buffers were not set forth in the Nichols paper. Although the lack of the precise numbers may prevent someone from duplicating exactly what Dr. Nichols did (Nichols Testimony, FR vol III, tab 10 at 40), the amount of citrate phosphate buffer was not critical to the experiment (Nichols Testimony, FR vol III, tab 10 at 59-60). Indeed, a fairly wide range of concentrations would result in accumulation and entrapment and a stable liposome. Accordingly, one skilled in the art would still be able to achieve a stable liposome having an enhanced catecholamine content. *Id.*

catecholamines. (Nichols Declaration at ¶ 13, FR vol II, tab 6 at 6-7; Prestegard Declaration at ¶ 13, FR vol II, tab 8 at 18).

41. The authors reported that "we observed a remarkable accumulation of each of the catecholamines tested." The uptake in concentration was twelve-fold over controls for norepinephrine, and eighteen- and twenty-three-fold, respectively, for epinephrine and dopamine. (Nichols Declaration at ¶ 10, FR vol II, tab 6 at 6).

42. The results are set forth in Figure 1 which demonstrates a gradual increase in catecholamine uptake to about sixty minutes and then a plateau from sixty to ninety minutes in which there was relatively little change for two of the three materials and an additional increase in the third compound. In deposition, Dr. Nichols characterized the change between sixty and ninety minutes to be "within the experimental error," although recognizing that there was a slight increase for all three materials. (Nichols Testimony, FR vol III, tab 10 at 45-46).

43. At 90 minutes, the pH gradient was destroyed by the addition of NH_4Cl and, due to the loss of the pH gradient, most of the catecholamines migrated out of the liposomes within 30 minutes. If the NH_4Cl had not been added, the pH gradient would have decayed over time, on the order of several hours, and the catecholamines would have leaked out over that time. (Nichols Testimony, FR vol III, tab 10 at 46-47 and 55-56).

The Cramer Reference

44. The reference, Cramer, J.A. and Prestegard, J.H., "NMR Studies of pH-InducedTransport of Carboxylic Acids Across Phospholipid Vesicle Membranes," Biochemical and

Biophysical Research Communications, 75(2):295-301 (1977) ("Cramer") (FR Exh 5), is prior art as to the Mehlhorn application.

45. According to Mehlhorn's declarant, Dr. Cafiso, Cramer discloses "the physical chemistry involved in using a pH gradient to load ionizable molecules into a liposome." (Second Cafiso Declaration at ¶ 3(c), MR 20; Third Cafiso Declaration at ¶ 3(i), MR 43).

46. As to the specifics of the Cramer disclosure, the paper reports the formation of liposomes in an aqueous solution of maleate buffer. A solution containing fumarate buffer (mostly in anionic form) was then added to the external liposome phase. Thereafter, an acid, specifically deuterated hydrochloric acid (DCl), was added to the external medium to lower the pH in the external phase, thereby creating a pH gradient, and to induce the formation of a neutral species from the initially negatively charged species. That neutral species then passed through the lipid bilayer into the aqueous internal phase. (Prestegard Declaration at ¶ 10-13, FR vol II, tab 8 at 16-18; Nichols Declaration at ¶ 14, FR vol II, tab 6 at 7-8).

47. The authors reported that:

> Figure 2 presents the [NMR] spectra observed when the external pH was lowered to 5.5 Lowering the outside pH serves to drive the transport of external fumaric acid into the interior of the vesicles.
>
> * * *
>
> Figures 3 and 4 reveal that adjusting the outside pH to a lower value (4.7 compared to 5.5) results in a rapid and greater accumulation of internal fumaric acid, followed by a slow simultaneous leakage of both acids.

(FR Exh 5, at pp. 297-98).

48. In deposition, Dr. Prestegard testified that he observed the accumulation of fumaric acid inside the liposome and that the liposomes exhibited a stability that is typical of liposome preparations. (Prestegard Testimony, FR vol IV, tab 11 at 105-06).

The Fendler Reference

49. The reference, J.H. Fendler, "Optimizing Drug Entrapment in Liposomes. Chemical and Biophysical Considerations," Liposomes in Biological Systems, Gregoriadis and Allison, eds., 1980, pp. 87-100 ("Fendler") (FR Exh 7), is prior art to the Mehlhorn application.

50. Fendler teaches the use of buffers to maintain pH gradients for extended periods of time to obtain more effective entrapment of drugs. (See Prestegard Declaration at ¶ 15, FR vol II, tab 8 at 19).

Forssen's claims 5, 6, and 25-27

51. Forssen's claims 5, 6, and 25-27[9] relate to a group of specific organic acids known as monofunctional pyranosidyl acids, including lactobionic acid and galacturonic acid, and their use in forming liposomes that contain doxorubicin. As set forth in the specification, Forssen discovered that monofunctional pyranosidyl acids can be used effectively to form liposomes in which anthracycline antineoplastic drugs, such as doxorubicin, can be loaded with a pH gradient. (Forssen specification, col 5, commencing at line 62).

52. Forssen also discovered that the use of the monofunctional pyranosidyl acids with doxorubicin resulted in liposomal compositions that were far less toxic than liposomal compositions made in citric acid. For example, in Example III, liposomal doxorubicin prepared in lactobionic acid resulted in a maximum tolerated dose (MTD) of 40 mg/kg

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[9] These claims read as follows:

5. A method as recited in claim 4 [which depends from claim 1] in which said organic acid is a monofunctional pyranosidyl acid.

6. A method as recited in claim 5 in which said pyranosidyl acid is lactobionic acid.

25. A method as recited in claim 1 in which said acid is lactobionic acid, said base is calcium carbonate, said diester is distearoyl phoshatidylcholine, said cationic, lipophilic drug is doxorubicin and cholesterol is present in the liposome bilayers as a stabilizer.

26. A method as recited in claim 25 in which the molar ratio of distearoyl phosphatidylcholine to cholesterol is about 2:1.

27. A method as recited in claim 1 in which said acid is galacturonic acid, said base is sodium carbonate, said diester is a mixture of distearoyl phoshatidylglycerol and distearoyl phosphatidylcholine, said cationic, lipophilic drug is doxorubicin and cholesterol is present in the liposome bilayers as a stabilizer.

while, in Example VIII, liposomal doxorubicin prepared in citric acid yielded a MTD of only 10 mg/kg. More significantly, the MTD of the citric acid-based doxorubicin liposome preparation is even less that the MTD of free doxorubicin: 25 mg/kg. Indeed, intravenous tests in mice demonstrated that doses of 20 mg/kg of free drug could be tolerated while equivalent doses of liposomal doxorubicin prepared from citric acid were lethally toxic (Col 10, lines 50-55).

ARGUMENT

I. Summary of the Argument

The Administrative Patent Judge acted properly and correctly in the October 4, 1996 Decision on Motions, and Mehlhorn will not be able to demonstrate that the APJ exhibited an abuse of discretion.

Mehlhorn's claims 27-50 are unpatentable under 35 U.S.C. §§ 102 and 103 in view of either the Nichols reference and/or the Cramer reference. The one-to-one correspondence between the elements of the claims and the references has been largely undisputed. Indeed, both Mehlhorn and its expert, Dr. Cafiso, recognize that both the Nichols and the Cramer references disclose "the physical chemistry involved in using a pH gradient to load ionizable molecules."

The point of dispute relates to Mehlhorn's contention that neither the Nichols nor the Cramer references disclose the preparation of "stable entrapped drug compositions." This contention ignores the literal language of the claims and seeks to add a limitation that has no support in the Mehlhorn specification.

There is no dispute that the independent claims 27 and 38 recite "charged chemical species," not "drug compositions." Moreover, Mehlhorn has admitted that there is no patentable

distinction between "charged chemical species" and drugs. Thus, the assertion of "drug compositions" cannot distinguish the references.

Mehlhorn's reliance on the stability of the liposome preparation as a point of distinction is equally unavailing. To the extent there is any support in the Mehlhorn specification for the concept of "stability," it means simply the retention of the species. The specification provides for "substantially maintaining the loaded chemical species within the vesicle for at least one-quarter hour following loading" and for a period of "15 minutes to several hours depending on the chemicals until the buffer leaks out of the vesicles." (Mehlhorn specification at pages 2-3, 6-7, and 14). The Nichols reference discloses retaining the accumulated liposomes for up to ninety minutes.

Should Mehlhorn seek a level of stability that is separate from the ninety minute retention time observed in the Nichols reference, that would be adding an extraneous limitation to the claims. Moreover, there is no support in the Mehlhorn specification for any parameter that would achieve that level of stability.

Accordingly, the APJ correctly found that Mehlhorn claims 27-50 are unpatentable to Mehlhorn, and his decision granting Forssen's motion for judgment should be affirmed.

The APJ also correctly found that Forssen claims 5, 6, and 25-27 are separately patentable. Those claims relate to a specific type of acid, the monofunctional pyranosidyl acids, for which Forssen demonstrated unexpected results, particularly with the anthracycline antineoplastic drug doxorubicin.

The toxicity of free doxorubicin, measured in a "maximum tolerated dose," is 25 mg/kg. In contrast, liposomal doxorubicin prepared in lactobionic acid (a type of monofunctional

pyranosidyl acid) yielded a much greater MTD: 40 mg/kg. Even more surprising, however, is the MTD observed with liposomal doxorubicin prepared in citric acid: a MTD of 10 mg/kg, indicating that the citric acid-based liposomal doxorubicin was more toxic than free doxorubicin.

Thus, the use of monofunctional pyranosidyl acids provides significant benefits compared to the commonly used citric acid. No one, prior to Forssen, however, recognized that the variation of the acid type would meaningfully alter the resultant drug-loaded liposome. Accordingly, Forssen's discovery that selecting a particular acid could positively effect the pH loading process and the resultant products is not *prima facie* obvious.

Moreover, the disclosure of the "potentially infinite" genus of acid buffers cannot render obvious the specific monofunctional pyranosidyl acids of Forssen claims 5, 6, and 25-27, particularly where there was absolutely no appreciation in the art of the importance of the acid buffer.

Accordingly, the APJ correctly found that Forssen claims 5, 6, and 25-27 are separately patentable and his decision granting Forssen's motion to redefine the interference should be affirmed.

II. The Administrative Patent Judge Has Not Exhibited an Abuse of Discretion

Mehlhorn will not succeed in demonstrating that the Administrative Patent Judge ("APJ") exhibited an abuse of discretion in the Decision on Motions of October 4, 1996. As set forth in 37 C.F.R. § 1.655(a), all interlocutory orders are presumed to be correct and the burden on the party attacking the order is an abuse of discretion. Mehlhorn cannot meet that standard here.

As defined by the Federal Circuit, an abuse of discretion may be found when

- the decision is clearly unreasonable, arbitrary or fanciful;

- the decision is based on an erroneous conclusion of the law;

- the findings are clearly erroneous; or

- the record contains no evidence upon which the decision could have been rationally based.

See *J.P. Stevens Co. v. Lex Tex, Ltd.*, 822 F.2d 1047, 1050, 3 U.S.P.Q.2d 1235, 1237, (Fed. Cir. 1987); *Western Elec. Co. v. Piezo Tech. Inc.*, 860 F.2d 428, 430-31, 8 U.S.P.Q.2d 1853, 1855 (Fed. Cir. 1988). As will be demonstrated below, Mehlhorn will not be able to demonstrate the October 4, 1994 Decision suffers any of these deficiencies.

III. Mehlhorn Claims 27-50 Are Unpatentable Under 35 U.S.C. §§ 102 and 103 in View of Nichols and/or Cramer

A. Introduction

In its Preliminary Motion for Judgment Under 37 C.F.R. § 1.633(a),[10] Forssen demonstrated a one-to-one correspondence between the disclosures of both the Nichols reference and the Cramer reference with each of the elements of the two independent claims of the Mehlhorn patent, on which all the subsequent claims depend.[11] Indeed, there is no need to discuss the dependent claims separately because Mehlhorn has never urged during this Interference that the dependent claims were separately patentable and is now foreclosed from so arguing by the express language of 37 C.F.R. § 1.655(b).[12]

Nonetheless, to ensure that there is no question as to the unpatentability of each of Mehlhorn's claims 27-50, Forssen submitted claim charts comparing each of the Mehlhorn claims to the Nichols and the Cramer references. For the convenience of the Board, those claim

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[10] Designated Motion 3 in the October 4, 1996 Decision on Motions.

[11] The additional elements of the dependent claims, i.e., buffers (claims 30-32 and 41-43); loading a drug (claims 33 and 44); loading a hydrophobic drug (claims 34-37 and 45-48) and specific conditions of pH (claims 49-50), are discussed collectively in this motion.

[12] 37 C.F.R. § 1.655(b) provides that:

> A party that fail to contest, by way of a timely filed preliminary motion under § 1.633(c), the designation of a claim as corresponding to a count, or fails to timely argue the separate patentability of a particular claim when the ground for unpatentability is first raised, may not subsequently argue to an administrative patent judge, or the Board, the separate patentability of claims designated to correspond to the count with respect to that ground.

charts, together with a detailed description of the claim comparisons, are reproduced in Appendix C.

In any event, the correspondence of the Mehlhorn claims to the references is largely undisputed.[13] Indeed, Mehlhorn's expert, Dr. David Cafiso, has acknowledged that the Nichols reference, as well as the Cramer reference, "discloses the physical chemistry involved in using a pH gradient to load ionizable molecules into a liposome." See Second Cafiso Declaration at ¶¶ 3(b) and 3(c), MR 18-19; Third Cafiso Declaration at ¶ 3(f), MR 39-40. Furthermore, Mehlhorn itself admitted that:

> Dr. Cafiso acknowledges that Nichols teaches that a drug composition can be accumulated into the liposome.

See Mehlhorn opposition to Forssen's contingent motion for judgment under 37 C.F.R § 1.633(a) that Mehlhorn claims 51-55 are unpatentable,[14] at page 4.

The remaining dispute revolves around the phrase "liposome-vesicle entrapped" charged species, with Mehlhorn arguing that the phrase connotes stable liposomes that are "capable of retaining species." *Id.* at 2. To distinguish the Nichols reference, Mehlhorn asserts that "there is no suggestion in Nichols and Deamer that a stable entrapped drug composition could be obtained as claimed by Mehlhorn." *Id.* at 4.

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[13] For example, Dr. Nichols testified that the only difference between the method described in the Nichols reference (FR Exh 3) and Mehlhorn claim 27 is that the entrapped species and base are added in the opposite order. (Nichols Declaration at ¶ 13, FR vol II, tab 6 at 6-7). Dr. Nichols further testified, however, that the sequence of these additions is unimportant. *Id.* Indeed, Mehlhorn does not contend that the sequence of the addition is of any patentable or technical significance.

[14] Designated Motion 6 in the October 4, 1996 Decision on Motions.

In seeking to distinguish the Nichols reference, however, Mehlhorn ignores basic tenets of patent law as well as the demonstration in Nichols of the stable retention of loaded catecholamines for up to ninety minutes.

B. Mehlhorn's Claims Cannot Be Interpreted as Claiming "Stable Entrapped Drug Compositions" to Distinguish over the Cited References

1. Mehlhorn's Independent Claims Recite "Chemical Species," and Both the Nichols and Cramer References Disclose "Chemical Species"

It cannot be disputed that Mehlhorn's independent claims 27 and 38 recite methods for preparing liposome-vesicle entrapped **chemical species**. Nonetheless, in comparing the claimed invention to the Nichols and Cramer references, Mehlhorn and its expert, Dr. Cafiso, repeatedly characterized the claimed invention as relating to "stable entrapped drug compositions." For example, in opposing Forssen's motion for judgment under 37 C.F.R. § 1.633(a),[15] Mehlhorn asserted that:

> Thus, there is no teaching or suggestion in Nichols and Deamer that a **stable entrapped drug composition** could be obtained **as claimed by Mehlhorn.** Nor would it have been obvious to one of ordinary skill in the art that a pH gradient could be used to prepare **stable entrapped drug compositions as claimed by Mehlhorn**.
>
> * * *
>
> There is no teaching or suggestion in and Cramer and Prestegard that a **stable entrapped drug composition** could be obtained **as claimed by Mehlhorn.** Nor would it have been obvious to one of ordinary skill in the art that a pH gradient could be used to prepare **stable entrapped drug compositions as claimed by Mehlhorn**.

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[15] Designated Motion 3 in the October 4, 1996 Decision on Motions.

Mehlhorn opposition at pp. 10-11 (emphasis added). Mehlhorn makes a similar argument in its opposition to Forssen contingent motion for judgment under 37 C.F.R. § 1.633(a).[16] Dr. Cafiso also advances such arguments in Third Declaration. (Third Cafiso Declaration at ¶3(i), MR 43-45).

In characterizing the claimed invention as a method to obtain stable entrapped drug compositions, however, Mehlhorn ignores a fundamental tenet of patent law: the invention must be limited to that which is claimed. *See Environmental Designs Ltd. v. Union Oil Co. of Calif.*, 713 F.2d 693, 699, 218 U.S.P.Q.2d 865, 871 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984). Both independent claims 27 and 38 claim "charged chemical species," not drugs or drug compositions or drug formulations or pharmaceutical preparations. Accordingly, to assess the patentabililty of these claims over the Nichols reference and the Cramer reference, one must consider whether those references disclose "charged chemical species." Whether or not the references also disclose the use of compounds uniformly recognized as drugs is simply irrelevant to the patentability of claims 27 and 38. It is also irrelevant to the patentability of any of the dependent claims that recite drugs, generically or specifically, because Mehlhorn admitted that there was no patentable distinction between "chemical species" and "drugs," as follows:

> Mehlhorn does not contend that limiting the charged chemical species to a lipophilic drug constitutes a separate patentable invention. Rather, the subject claims are included to emphasize that the same patentable invention is being claimed in both the Mehlhorn application and the '683 patent.

Prosecution History of USSN 07/741,305, Paper No. 3, Request by Applicant for Interference Pursuant to 37 C.F.R. § 1.607 of August 7, 1991, at 9.

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[16] Designated Motion 6 in the October 4, 1996 Decision on Motions.

Thus, when the proper terms are compared, there is no dispute that the Nichols reference and the Cramer reference disclose the methods of Mehlhorn's claims 27-50, the preparation of liposomes that accumulate charged chemical species via a pH gradient. Moreover, Mehlhorn concedes, as it must, that the catecholamines of Nichols are drugs. See Third Cafiso Declaration at ¶ 3(c), MR 36.

2. Mehlhorn's Claims Recite "Vesicle-Entrapped" Chemical Species, and Both the Nichols and Cramer References Disclose "Entrapped Chemical Species"

To avoid the Nichols and Cramer references, as noted above, Mehlhorn and its expert, Dr. Cafiso, characterize the claimed invention as relating to "stable" drug entrapped preparations. In opposing Forssen's contingent motion for judgment that Mehlhorn proposed claims 51-55 are unpatentable,[17] Mehlhorn explains its claim construction theory that leads to the term "stable" which, of course, is no where to be found in any of Mehlhorn's claims 27-50. According to Mehlhorn, the only reasonable interpretation of "vesicle-entrapped charged species" is that they be stable, i.e., capable of retaining species, because to do otherwise would be "nonsensical" and would go "completely against the whole teaching of the application" and against the "only reasonable interpretation" by a person skilled in the art.

That a liposome that is intended to entrap a chemical species is also intended to retain that chemical species for a limited period of time is logical and acceptable to Forssen. Mehlhorn seeks, however, a more specific definition of stable, one that excludes a liposome that retains a

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[17] Designated Motion 6 in the October 4, 1996 Decision on Motions.

chemical species for up to ninety minutes. If anything is nonsensical, it is that theory of claim construction.

a. The Nichols Liposome Preparations Exhibited Stable Entrapment of Catecholamines for up to Ninety Minutes

As set forth above in the Statement of Facts, the Nichols reference describes forming liposomes in citric acid, adding a base to the external phase to create a pH gradient, introducing one of three catecholamines, and observing "remarkable accumulation of each of the catecholamines tested." In his declaration, Dr. Nichols characterized the results as follows:

> In fact, as illustrated in Figure 1 on page 270 of our publication [FR Exh 3], Dr. Deamer and I achieved stable uptake of the three catecholamines for 90 minutes.

(Nichols Declaration at ¶ 7, FR vol II, tab 7 at 12).

Figure 1 depicts a gradual increase in catecholamine uptake[18] to about sixty minutes and then a plateau from about sixty to ninety minutes in which any observed change was within "experimental error." (Nichols Testimony, FR vol III, tab 10 at 45-46). The increases in

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[18] The authors did note that it was "interesting that the uptake of catecholamine is relatively slow. For instance, the monoamine 9-aminoacridine reaches equilibrium within seconds under similar conditions." They attributed the difference in rate to the hydroxyl groups on the catecholamines which would limit their "permeability to lipid bilayer membranes." See FR Exh 3 at 271, third full paragraph.

This comports with Mehlhorn's description of the rate of uptake which states:

> The chemical's loading rate will depend on the pKa and will be complete within less than a minute for low molecular weight (MW less than 500) amine chemicals with pKas less than 10 and having no charge or strongly polar groups other than the amino group. Analogously, weak acids having pKas greater than 4 will accumulate in the liposome in about one minute unless they bear strongly polar groups other than their carboxyls.

Mehlhorn specification, Detailed Description, at 13, lines 13-21.

concentration ranged from twelve-fold for norepinphrine, eighteen-fold for epinephrine, and twenty-three-fold for dopamine.[19] (*Id.*) After the pH gradient was destroyed at ninety minutes, the catecholamines migrated out of the liposomes, with most of the catecholamines out within thirty minutes. (Nichols Testimony, FR vol III, tab 10 at 46-47).

Because the catecholamine concentration increased to a plateau (Nichols Testimony, FR vol III, tab 10 at 42), with no indication of decreasing concentration, or at the very least approached a "stable asymtope" (Nichols Testimony, FR vol III, tab 10 at 45), one can only conclude that whatever catecholamine was entrapped within the liposome was retained within the liposome for up to ninety minutes, until the force driving the accumulation, the pH gradient, was destroyed. Indeed, Dr. Nichols testified that his paper reflected that he and Dr. Deamer had achieved stable liposomes having enhanced catecholamine content for at least ninety minutes, recognizing, of course, that the amount of catecholamines would have gradually decayed over several hours had the pH gradient not been intentionally destroyed at ninety minutes. (Nichols Testimony, FR vol III, tab 10 at 46-47 and 55-56).

Dr. Prestegard similarly described the results of the Nichols paper. He characterized the paper as "teaching loading and retention of material in liposomes over time," (Prestegard Testimony, FR vol IV, tab 11 at 85), even though there was no attempt to measure retention

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[19] The Nichols paper does express some surprise at these levels of accumulation, noting that it was a "fraction" of that expected for an "ideal monamine responding to a 3 pH unit gradient." See Exh 3 at p. 271, second full paragraph. This comports with the discussion in the Mehlhorn specification regarding the expectation of a ten-fold accumulation for every unit of pH difference. See Mehlhorn specification, Detailed Description, at p. 11, first full paragraph.

beyond the plateau observed between sixty and ninety minutes (*Id.* at 85-86).[20] In addition, even though Dr. Prestegard recognized that the apparent intent of the research was not the maintenance of an entrapped drug, (*Id.* at 86-87), he maintained his belief that the Nichols catecholamine-entrapped liposome preparation exhibited stability over roughly 90 minutes. (*Id.* at 106-107).

Thus, should the "liposome-vesicle entrapped chemical species" mean a stable vesicle, the Nichols reference supplied precisely that. Indeed, the Nichols liposome preparations were more that six times more stable than those described in the Mehlhorn application. Specifically, rather then maintaining the species for fifteen minutes after loading, as is described in the Mehlhorn specification, the Nichols reference teaches that the catecholamines were maintained within the liposomes for up to ninety minutes after loading.

b. Nothing in the Claims Requires Any Particular Level of Stability, nor Are There Any Claim Parameters that Would Confer Any Particular Level of Stability

To read any of the Mehlhorn claims to require a level of stability beyond the up-to-ninety minute stability observed with the Nichols liposomes would contravene two basic tenets of patent law:

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[20] Dr. Prestegard also acknowledged that, while a person skilled in this art could extrapolate from the Nichols disclosure the loading of other specific drugs into liposome via a pH gradient (Prestegard Reply Declaration at ¶ 4, FR vol II, tab 9 at 24), there may be factors with certain compounds that are outside the bounds of reasonable extrapolation (Prestegard Testimony, FR vol IV, tab 11 at 91). Nonetheless, he reaffirmed his belief that Nichols did obtain a stable liposome with enhanced accumulation of catecholamines that exhibited stability for roughly ninety minutes. (Prestegard Testimony, FR vol IV, tab 11 at 106-107.

- it would add an extraneous limitation to the claim merely to avoid the prior art, as opposed to aiding in the interpretation of a claim, *E.I. du Pont de Nemours & Co. v. Philips Petroleum Co.*, 849 F.2d 1430, 1434, 7 U.S.P.Q.2d 1129, 1132 (Fed. Cir. 1988); and

- it would lack any written description support in the specification in violation of the requirements of 35 U.S.C. § 112, first paragraph, *In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983).

Should the term "stable" be introduced into the Mehlhorn claims, it must be only in an effort to interpret the claims. If it is not necessary for interpretation, the term would be an improper extraneous limitation. Moreover, if added as part of such interpretation, the term can only have a meaning that is described in the specification. As set forth above in the Statement of Facts, the Disclosure of the Invention of the Mehlhorn specification repeatedly describes "substantially maintaining the loaded chemical species within the vesicle for at least one-quarter hour following loading."[21] See Mehlhorn specification, pp. 2-3 and 6-7. More specifically, the Detailed Description provides that:

> After incorporation the chemical will remain in the vesicle for fifteen minutes to several hours depending on the chemicals, until the buffer leaks out of the vesicles. (Mehlhorn specification, p. 14, first full paragraph).

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[21] Maintaining the loaded species within the liposomes for time periods as short as fifteen minutes is acceptable because, as Mehlhorn explains, "degradation of the vesicles and leakage of the chemicals prior to administration need not be a concern since" the liposomes can be prepared shortly before use. Mehlhorn specification, Disclosure of the Invention, p. 7-8. Thus, stability over a long period of time is not required. Indeed, Mehlhorn touts the ready release from the liposome of the loaded species as an advantage in drug delivery systems. *Id.*

Accordingly, if added, the term can only refer to a liposome that can retain the chemical species for "15 minutes to several hours." A retention time of up to ninety minutes falls clearly within this range.

Furthermore, if Mehlhorn continues to argue for another level of stability, the claims must be examined for any parameter that would lead to such a level. In fact, there is none. Indeed, there can be no such parameter because there is no support for such a parameter. There is simply nothing in the Mehlhorn specification that teaches anything about obtaining liposomes having an enhanced concentration of the desired chemical species within the liposome beyond that set forth in the Nichols and the Cramer references. As Dr. Prestegard testified, "I saw nothing that describes a method that addresses any enhancement over stability obtained in either of the previous papers [the Nichols paper and the Cramer paper]." (Prestegard Testimony, vol IV, tab 11 at 107-08). If such a parameter is added, it would be wholly without support in the Mehlhorn specification.

C. Conclusion

Accordingly, whether or not Mehlhorn's claim construction leading to "stable entrapped drug composition" is correct, it cannot distinguish any of the Mehlhorn claims from the teaching in the Nichols reference. The Administrative Patent Judge correctly found that the Mehlhorn claims 27-50 were unpatentable under 35 U.S.C. §§ 102 and 103 over the Nichols reference and the Cramer reference.

IV. Forssen Claims 5, 6, and 25-27 Define an Invention that Is Separately Patentable from the Other Claims Designated as Corresponding to the Count

A. The Discovery of the Unexpected Advantages of Monofunctional Pyranosidyl Acids

As has been widely reported, anthracycline antineoplastic drugs are highly toxic when administered *in vivo*. Thus, while doxorubicin and daunorubicin are the drugs of choice for the treatment of most advanced malignancies, their utility is severely limited as to the amount and frequency of the dose, due to their cardiotoxicity. To reduce toxicity, it is very desirable to be able to deliver the drugs in liposomal form.

As set forth in the Forssen patent (column 2, lines 15 *et seq.*), however, the usefulness of liposomes as a delivery system for anthracycline antineoplastic drugs has been limited by the absence of a method of preparation that is capable of incorporating sufficient quantity of the drug to be effective in the treatment and at the same time providing a drug preparation with the necessary reduced cardiotoxicity of the drug. Accordingly, while the prior art, as represented by the Nichols and Cramer publications identified above, disclosed the use of a pH gradient with certain acids to load drugs and other chemicals into liposomes, it did not disclose or recognize the need for, nor suggest, the use of different types of acids in a method of preparing liposomes, particularly those containing anthracycline antineoplastic drugs.

Forssen discovered (see e.g., column 5, commencing at line 62), that monofunctional pyranosidyl acids, e.g., lactobionic and galacturonic acid, can be used very effectively to form liposomal compositions, particularly such compositions in which anthracycline antineoplastic drugs are loaded into the liposomes, using a pH gradient.

Thus, Forssen found that doxorubicin could be loaded into liposomes with lactobionic and galacturonic acids, but **not** by acetic acid. Forssen also discovered that, when citric acid was used, the resulting doxorubicin liposomes were far **more** toxic than the free drug. Indeed, as set forth in example VIII (column 10, line 19 *et seq.*), liposomal doxorubicin formed in citric acid resulted in liposomal doxorubicin having a maximum tolerated dose (MTD) of only 10 mg/kg, which is far less than the MTD of free doxorubicin of 25 mg/kg. In sharp contrast, liposomal doxorubicin prepared in lactobionic acid as in Example III resulted in a maximum tolerated dose of 40 mg/kg, an improvement of some **300%** over liposomal doxorubicin prepared form citric acid and 60% better than the reported MTD of the free drug. Intravenous tests in mice with such compositions demonstrated that while doses of 20 mg/kg of the free drug could be tolerated, equivalent doses of liposomal doxorubicin prepared form citric acid were lethally toxic (column 10, lines 50-55).

B. The Test for a Separately Patentable Invention

37 C.F.R. 1.601(n) sets forth the definition of separately patentable inventions in an Interference:

> Invention "A" is a "separate patentable invention" with respect to invention "B" when invention "A" is new (35 U.S.C. 102) and non-obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A".

See also *In re Van Geuns*, 988 F.2d 1181, 1185, 26 U.S.P.Q.2d 1057, 1060 (Fed. Cir. 1993).

1. Forssen Claims 5, 6, and 25-27 Are Novel

As indicated by the discussion above, claims 5, 6, and 25-27 of the Forssen patent define an invention that is novel and nonobvious and, accordingly, patentable. There is no description in the prior art of the use of a monofunctional pyranosidyl acid to prepare liposomes and load a drug, particularly anthracyclines antineoplastic agents, into such liposomes using a pH gradient. Hence, the subject matter of these claims is novel and satisfies fully the conditions for patentability of 35 U.S.C. § 102.

2. Forssen Claims 5, 6, and 25-27 Are Nonobvious

By the same token, the subject matter is nonobvious and fulfills the conditions for patentability of 35 U.S.C. § 103. The differences between the claimed invention and the prior art are clear and significant, such that the subject matter as a whole would not have been obvious to one of ordinary skill in the liposome art at the time the invention was made.

In *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966), the Supreme Court set forth the test for determining obviousness:

> Under 103, [1] the scope and content of the prior art are to be determined; [2] differences between the prior art and the claims at issue are to be ascertained; and [3] the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long-felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. (383 U.S. at 17-18.)

In assessing obviousness in light of this decision, particularly unique aspects of the invention bear discussing first.

a. The Use of M nofunctional Pyran sidyl Acids Is Not *Prima Facie* Obvious from the Prior Art

When the prior art fails to recognize that a particular parameter or variable is result-effective, that is, that variation of the parameter meaningfully alters the results, the art cannot establish a *prima facie* case of obviousness for processes wherein that parameter has been altered or optimized. *In re Yates*, 663 F.2d 1054, 1056, 211 U.S.P.Q. 1149, 1151 (C.C.P.A. 1981); *In re Antonie*, 559 F.2d 618, 620, 195 U.S.P.Q. 6, 8-9 (C.C.P.A. 1977).

This rule is clearly applicable to the case here. Prior to Forssen's discovery, those skilled in the art did not recognize that selection of the species of acid used in pH loading of drugs into liposomes could exert a meaningful affect on the resultant drug-loaded liposomes. Accordingly, Forssen's discovery that selecting a particular acid could positively effect the pH loading process and the resultant products is not *prima facie* obvious.

This conclusion is fully supported by the evidence of record. For example, the "prior art" for purposes of this motion (i.e., Forssen claim 1 designated as corresponding to the Count) generically recites only "acid." The other claims designated as corresponding to the Count likewise fail to suggest that the acid species is a result-effective variable. None of the other art cited in this Interference teaches or suggests that the material acid species might be a result effective variable.

b. The Disclosure of the Genus Acid Does Not Render Obvious the Species of Monofunctional Pyranosidyl Acids

It is well established that the fact that a compound may be encompassed by a disclosed genus does not, by itself, render that compound obvious. *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). Indeed, in *Jones* the Court has expressly declined "to

extract from *[Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 806-09, 10 U.S.P.Q.2d 1845, 1845-48 (Fed. Cir. 1989) *cert. denied*, ___ U.S. ___, 110 S. Ct. 498 (1989)] the rule . . . that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it." *Id.* at 350, 21 U.S.P.Q.2d at 1943. Rather, the Court counseled that each case of obviousness must necessarily be decided upon its own facts. *Id.*

Moreover, one of the facts that must be evaluated in determining whether a species is obvious over a disclosed genus is the relative size of the genus. *Id.* In *Jones*, the Court reversed a finding of obviousness, in part, because the prior art genus encompassed a "potentially infinite genus" of compounds. This consideration is particularly applicable to the present case. The pertinent "prior art" (*i.e.*, Forssen's claim 1) discloses the genus of acids. Acids, however, include any compound having an ionizable hydrogen atom. Thus, much like the genus in *Jones*, the genus disclosed by the "prior art" here is potentially infinite and includes literally millions of widely varying compounds.[22] Under such circumstances, it cannot be said that selection of the particular species of monofunctional pyranosidyl acids is obvious. *See also In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993).

Another fact that must be evaluated is what the prior art fairly suggests. When the prior art suggests a preference leading **away from** the claimed species, the disclosure of a genus does

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[22] For example, the genus acids includes "inorganic acids" and "organic acids," the latter of which encompasses not only all of the groups of acids disclosed at column 5, lines 43-59, of the Forssen Patent (including amino acids, alpha-hydroxy polycarboxylic acids, saturated and unsaturated, unsubstituted and substituted aliphatic dicarboxylic acids, and phosphorus-containing organic acids and the like), but also, any other carbon-containing acid.

not render obvious the claimed species. *In re Baird*, 16 F.3d 380, 383, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994).

The prior art as embodied in the Mehlhorn specification leads away from the invention. The specification lists only three species of acid: citric acid, succinic acid, and tartaric acid. Citric acid is an alpha-hydroxy polycarboxylic acid; succinic and tartaric acids are saturated and unsaturated, unsubstituted and substituted aliphatic carboxylic acids. Thus, considering Mehlhorn's specification as illustrative of the state of the art, there is no suggestion in the "prior art" of monofunctional pyranosidyl acids.

Rather, the "prior art" suggests a distinct preference for two fundamentally different classes of acids: the alpha-hydroxy polycarboxylic acids and the saturated and unsaturated, unsubstituted and substituted aliphatic carboxylic acids. Such a suggestion leading away from the subject matter claimed by Forssen, in combination with the nearly infinite scope of the genus of acids, is strongly probative of the nonobviousness of selecting the monofunctional pyranosidyl acids over the "prior art" genus of acids.

c. Forssen Has Shown that the Invention Claimed in Claims 5, 6, and 25-27 of the Forssen Patent Gives Rise to Unexpected Results

(1) Forssen Has Compared the Monofunctional Pyranosidyl Acids to the Closest Prior Art

In presenting evidence to establish unexpected results, one need only compare the claimed invention with the closest prior art. *Ex parte Gelles*, 22 U.S.P.Q.2d 1318, 1319 (Bd. Pat. App. & Int. 1992). For chemical compounds, the closest prior art is the prior art compound that is closest structurally to the claimed compound or compounds. *In re Kuderna*, 426 F.2d 385, 165

U.S.P.Q. 575 (C.C.P.A. 1970). Forssen has compared the claimed monofunctional pyranosidyl acids to the closest "prior art", i.e., the acid suggested by the "prior art" that is closest structurally to the monofunctional pyranosidyl acids -- citric acid, an alpha-hydroxy polycarboxylic acid.

As noted above, Mehlhorn's specification discloses only three species of acid (citric acid, succinic acid, and tartaric acid) and only citric acid is used in Mehlhorn's examples. Citric acid is an alpha-hydroxy polycarboxylic acid, while succinic acid and tartaric acid are saturated and unsaturated, unsubstituted and substituted aliphatic carboxylic acids. *See* Forssen Patent, column 5, lines 49-57. Alpha-hydroxy polycarboxylic acids are closer structurally to the monofunctional pyranosidyl acids than are saturated and unsaturated, unsubstituted and substituted aliphatic carboxylic acids.

This conclusion is supported by Mehlhorn's expert, Dr. Cafiso, who states that the monofunctional pyranosidyl acids are useful for pH loading by virtue of the hydroxyl groups on these acids. (Second Cafiso Declaration at ¶ 4 (d), MR 28-29). Similarly, the alpha-hydroxy polycarboxylic acids, by definition, also bear at least one hydroxyl group. Conversely, however, the saturated and unsaturated, unsubstituted and substituted aliphatic carboxylic acids may or may not contain a hydroxyl group.

Dr. Cafiso also states that the presence of other functional groups on the acid may influence its properties as the internal acid for pH loading. (Second Cafiso Declaration at ¶ 4(c), MR 28). Alpha-hydroxy carboxylic acids, like the monofunctional pyranosidyl acids, do not contain any functional groups other than hydroxyl and carboxylic acids groups. But the saturated and unsaturated, unsubstituted and substituted aliphatic carboxylic acids may possess a number of other functional groups that will affect their properties in pH loading. For example, the

saturated and unsaturated, unsubstituted and substituted aliphatic carboxylic acids may contain an oxo moiety, such as ketoglutaric acid, or unsaturation, such as maleic acid or fumaric acid. Forssen Patent, column 5, lines 53-57.

Citric acid is therefore much closer structurally to the monofunctional pyranosidyl acids than a saturated and unsaturated, unsubstituted and substituted aliphatic carboxylic acid. By comparing the monofunctional pyranosidyl acids with citric acid, Forssen has compared the claimed invention with the closest "prior art" compound, citric acid.

Furthermore, there is no burden to test a multiplicity of prior art compounds. Indeed, if evidence is presented showing the superiority of a claimed compound over the prior art compound that is structurally most similar, such unobviousness need not be confirmed by a comparison with compounds that are less structurally similar. *In re Kuderna*, 165 U.S.P.Q. 575 (C.C.P.A. 1965).

(2) Forssen's Results Are Unexpected

As noted above, Forssen has presented evidence that the results obtained with monofunctional pyranosidyl acids were unexpected to one of ordinary skill. At column 5, line 69, to column 6, line 5, of the Forssen patent, Forssen discloses that "[c]itric acid has also been found to entrap doxorubicin, but **surprisingly** the resulting loaded vesicles provide to be **far more toxic** than the free drug" (emphases added). Forssen further discloses that, in contrast, liposomes loaded with doxorubicin using a monofunctional pyranosidyl acid were less toxic than the free drug.

This disclosure is contained in an issued United States patent and is therefore, evidence cognizable in this interference proceeding. 37 C.F.R. § 1.639. Thus, Forssen has presented evidence of the views of a worker of at least ordinary skill.

(3) The Showing of Unexpected Results Obtained with Monofunctional Pyranosidyl Acids Is Commensurate in Scope with Claims 5, 6, and 25-27

The unexpected results disclosed above can reasonably be extrapolated to the rest of the monofunctional pyranosidyl acids. As noted by Dr. Cafiso, the monofunctional pyranosidyl acids all share the same common structural features that may affect utility as the internal acid, i.e., a single ionizable hydrogen atom and a plurality of hydroxy groups. None of the monofunctional pyranosidyl acids contain other functional groups that might affect their properties as the internal acid. Accordingly, there is no reasonable basis for not extending the showing of unexpected results presented in the Forssen patent to the subgenus of monofunctional pyranosidyl acids.

Finally, Forssen is not required to test every species within the claimed sub-genus of monofunctional pyranosidyl acids. *Ex parte Winters*, 11 U.S.P.Q.2d 1387, 1388 (Bd. Pat. App. & Int. 1989) (finding comparison of a single compound within the scope of the claimed genus to its closest prior art counterpart adequately representative to establish unexpected results for the claimed genus). Indeed, so long as Forssen has compared a representative member of the claimed subgenus to the closes prior art compound, nothing more is needed. *Id.* at 1388. As shown above, Forssen has complied with this requirement.

C. Conclusion

Thus, for the foregoing reasons, Forssen claims 5, 6, and 25-27 are separately patentable. The Administrative Patent Judge correctly found that the Forssen claims should be designated as not corresponding to the count.

CONCLUSION AND RELIEF REQUESTED

For the foregoing reasons, the party Forssen respectfully submits that claims 27-50 (as well as proposed claims 51-55) of the Mehlhorn application are unpatentable to Mehlhorn as being anticipated or rendered obvious by the prior art, including the Nichols and Cramer references, and that Forssen claims 5, 6, and 25-27 do not correspond to the count.

Accordingly, Forssen respectfully requests that the October 4, 1996, Decision on Motions by Administrative Patent Judge Ronald H. Smith be affirmed and that judgment be awarded to Forssen.

Respectfully submitted,

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Date: July 10, 1997

CERTIFICATE OF SERVICE

I hereby certify that a copy of the attached paper, "JUNIOR PARTY FORSSEN'S OPENING BRIEF FOR FINAL HEARING UNDER 37 C.F.R. § 1.656," including the exhibits, is being served upon the Senior Party, Rolf J. Mehlhorn, in accordance with 37 C.F.R. § 1.646, this 10th day of July, 1997, via Federal Express, fees prepaid, to the lead attorney for the Senior Party at the following address:

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